L. Silver (purged)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

T1401M

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

CORRECTED COPY

WARNING LETTER

VIA FEDERAL EXPRESS

JAN 27 1998

Mr. Hiroshi Kinoshita
Manager, Medical Devices Factory
Nikkiso Co., Ltd.
3-43-2, Ebisu, Shibuya-ku
Tokyo, 150-91, Japan

Dear Mr. Kinoshita:

During the Food and Drug Administration's (FDA) inspection of your firm, Shizouka Plant, located at 98-1, Shizutani Haibara-cho, Haibara-gun, Shizouka, 421-4, Japan, from August 25-29, 1997, our investigator determined that your firm manufactures hollow fiber hemodialyzers. Hemodialyzers are devices within the meaning of Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

The above-stated inspection revealed that these devices are adulterated, in that the methods used in, or the facilities or controls used for the manufacture, packaging, storage, or installation are not in conformance with the Quality System Regulations, as specified in Title 21, Code of Federal Regulations (21 CFR), Part 820, as follows:

1. Failure to validate a process with a high degree of assurance where the results of the process cannot be fully verified by subsequent inspection and test, as required by 21 CFR 820.75(a). For example, validation of the [redacted] process did not include any determination of whether sterilization has had an adverse effect on the functionality of the [redacted]. As a part of validating a manufacturing process, product qualification should be conducted to determine whether the manufactured product meets its performance requirements. When validating a sterilization process, especially [redacted], product qualification should include a determination of whether sterilization has had any affect on the product's functionality.

2. Failure to validate computer software for its intended use according to an established protocol when software is used as part of production or the quality system, as required by 21 CFR 820.75(j). For example, the software used to perform [redacted] has not been validated. This software is part of the quality system and controls the [redacted]. Your management indicated to the investigator that its personnel did not have the knowledge to validate or test the software and would have to be trained in the area.

3. Failure to conduct finished device acceptance procedures to ensure that each production run, lot, or batch of finished devices meets acceptance criteria, as required by 21 CFR 820.80(d). For example, [redacted] are the only functional tests performed, and these tests are performed during manufacturing. No functional tests are

performed on finished devices. Approximately [redacted] complaints concerning [redacted] have been received from October 3, 1996, to August 1997.

4. Failure to verify or validate the corrective and preventive action to ensure that such action is effective and does not adversely affect the device, as required by 21 CFR 820.100(a)(4). For example, there was no validation or testing performed to ensure that the [redacted], implemented as corrective action to [redacted], would be effective, or have an effect on the performance of the device. The change was implemented as a result of complaints received relating to [redacted] Additionally, the change appears to have been implemented prior to formal management approval. Records showing the first lot containing the change (manufactured by the sister facility, [redacted]) was manufactured on April 7, 1997, but approval date was documented on April 23, 1997.

5. Failure to establish a quality plan which defines the quality practice, resources, and activities relevant to devices that are designed and manufactured, and establish how the requirements for quality will be met, as required by 21 CFR 820.20(d). For example, the procedure which discusses [redacted] does not contain the required elements such as resources and activities relevant to the referenced devices or does not show how the requirements for quality will be met, as required for a quality plan.

6. Quality audits are inadequate to assure that the quality system is in compliance with the established quality system requirements and to determine the effectiveness of the quality system, as required by 21 CFR 820.22. For example, internals audit are inadequate to ensure the quality system is in compliance with production and processing controls, purchasing controls, statistical techniques, and personnel training. Although an October 1996, internal audit covered the above mentioned areas, this FDA inspection revealed significant deficiencies in the same. The most recent internal audit was conducted in May 1997.

7. Failure to evaluate and select potential contractors on the basis of their ability to meet specified requirements, including quality requirements; define the type and extent of control to be exercised over the product and contractor, based on the evaluation results; and establish and maintain records of acceptable contractors, as required by 21 CFR 820.50. For example:

   a. You have not established the requirements that must be met by your supplier, [redacted], the sister facility which provides the [redacted]; and [redacted] for the [redacted]. Your management reportedly stated that meetings are held with the vendors to agree on such requirements, however, no documentation of such requirements were noted.

b. There are no documented evaluations of suppliers describing the firm's assessment of the suppliers or component vendors. In addition to the [redacted] your suppliers include [redacted] for [redacted] for [redacted] for [redacted] and [redacted] for [redacted]

c. The type and control to be exercised over the suppliers and product have not been defined.

8. Failure to base sampling plans on a valid statistical rationale, as required by 21 CFR 820.250(b). For example:

a. There is no rationale for the established criteria of [redacted] cutoff for the [redacted]. Investigations of sample failures are not conducted until the failure rate reaches [redacted]

b. For the pressure test performed on [redacted] received, you have established [redacted] cutoff failure rate. For every [redacted], if [redacted] of the [redacted], the lot is rejected. You reportedly claim the [redacted] was obtained from the vendor and do not know the statistical rationale for it.

This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Act and regulations. The specific violations noted in this letter and in the FDA 483 issued at the close of the inspection may be symptomatic of serious underlying problems in your firm's manufacturing and quality assurance systems. You are responsible for investigating and determining the causes of the violations identified by the FDA. If the causes are determined to be systems problems, you must promptly initiate permanent corrective actions. Federal agencies are advised of the issuance of all Warning Letters about devices so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct these and any other manufacturing or quality systems deviations identified by your internal audits. Failure to promptly correct these deviations may be identified in a follow-up inspection, and may result in the detention of your device(s) without physical examination upon entry into the United States.

Please notify this office, in writing, within 15 working days of receipt of this letter of the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to identify and make corrections to any underlying systems problems necessary to assure that similar violations will not recur. Please include any and all documentation to show that adequate correction has been achieved. In the case of future

corrections, an estimated date of completion, and documentation showing plans for correction, should be included with your response to this letter. If the documentation is not in English, please provide a translation to facilitate our review. Please address your response and any questions to Timothy R. Wells, Chief, OB/GYN, Gastroenterology and Urology Branch, at the letterhead address.

Should you require any assistance in understanding the contents of this letter, do not hesitate to contact Ms. Sharon Murrain-Ellerbe at the letterhead address or at (301) 594-4616 or FAX (301)594-4638.

Sincerely yours,

James L Woods for

Lillian J. Gill
Director
Office of Compliance
Center for Devices and
Radiological Health